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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,866	06/26/2000	Avi J Ashkenazi	P1761R1	2405

7590 05/21/2002

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EXAMINER
LAZAR WESLEY, ELIANE M

ART UNIT	PAPER NUMBER
1646	15

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/603,866	Ashkenazi
Examiner	**Art Unit**
Eliane Lazar-Wesley	1646

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Mar 11, 2002*.

2a) This action is **FINAL.** 2b) X This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-11 and 49-54* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *1-11 and 49-54* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)	Notice of References Cited (PTO-892)	4)	Interview Summary (PTO-413) Paper No(s).
2)	Notice of Draftsperson's Patent Drawing Review (PTO-948)	5)	Notice of Informal Patent Application (PTO-152)
3) X	Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4,5,6,7,8	6)	Other:

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-11 and 49-54, in Paper No. 14 filed March 11, 2002, is acknowledged.

Pending claims 1-11 and 49-54 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-5 and 7-11, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a formulation comprising Apo-2 ligand, without providing the metes and bounds of what an Apo-2 ligand is. The claim is indefinite, because the name of a protein does not define it in terms of structure or function. In fact, the name of a protein is arbitrarily assigned by the inventors thereof, and may change over time as more is discovered about the protein. For example, interleukin-1 is also known as lymphocyte activating factor, endogenous pyrogen, leucocyte endogenous mediator, mononuclear cell factor, and catabolin (see Callard et al, The Cytokine FactsBook, Academic Press Ltd, 1994, page 31).

Claim 7 recites a biologically active fragment or variant of Apo-2 ligand of SEQ ID No:1. The claim is indefinite, as it is not clear what biological activity is referred to, and what is

encompassed by "a variant". For example, a biological active fragment could be a 6 or 8 amino acid long fragment able to generate an immunogenic response. The specification indicates that Apo-2 ligand is involved in apoptotic cell death (page 2, lines 20-21 for example). The specification also discloses alanine substitution variants having variable apoptotic activity (see Table I and Example 4). However, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 6 is objected to as depending on a rejected claim.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 5-11, and 49-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a formulation comprising one or more divalent ions, said ions being zinc or cobalt, wherein the concentration of said divalent ions in the formulation is at a <2X molar ratio to Apo-2 ligand, does not reasonably provide enablement for a formulation comprising other divalent ions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 5-11, 49 and 52-54, recite a formulation comprising one or more divalent ions, wherein the concentration of said divalent ions in the formulation is at a <2X molar ratio to Apo-2

ligand. The specification discloses a formulation comprising zinc or cobalt at a <2X molar ratio to Apo-2 ligand. However, the specification does not disclose formulations comprising other specific divalent ions, and does not support that other divalent ions have the same property as zinc or cobalt, for example in contributing to improve the production and recovery of Apo-2 ligand (Examples 8 and 9), and the specification does not recite how to make a formulation wherein the divalent ion other than zinc or cobalt is present at a <2X molar ratio to Apo-2 ligand, and confers a particular property to Apo-2 ligand. The specification shows that the metals bound to Apo-2 ligand are zinc and cobalt (Example 5). However, the other divalent ions tested, Cd, Ni and Cu, do not bind to Apo-2L, and it does not appear that divalent cations other than Zn or Co bind to Apo-2L , and that formulations containing divalent ions other than Zn or Co confer any particular property to Apo-2L. The specification is not commensurate with the scope of the claims.

Furthermore, claims 49-54 recite a formulation wherein the polypeptide present in the formulation is a fragment of the Apo-2L of SEQ ID No:1 which induces apoptosis or binds to Apo-2L receptor. Claim 7 is to a formulation comprising a variant of the Apo-2L of SEQ ID No:1. The specification does not disclose which fragment induces apoptosis or binds to Apo-2L receptor, and if the presence of divalent ions in the formulation has an effect on such fragments, or on which variant . As Apo-2L is active as a trimer to which Zn is bound, it is unpredictable which fragment or variant will allow for making an Apo-2L trimer to which Zn or Co binds, and considering the lack of guidance and working example, and the state of the art, it would constitute undue experimentation to make/use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-11 and 49-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Wiley, Immunity 3:673-682, December 1995, cited by Applicants.

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Wiley, Immunity 3:673-682, December 1995, discloses the purification of soluble TRAIL (page 680). TRAIL is identical to the Apo-2 ligand of SEQ ID No:1 (see sequence comparison, attached). The fractions resulting from the purification step were eluted in 50mM Na citrate. According to Applicant's own admission, in Example 5, Apo-2L has one binding site per trimer, and the site is occupied with metal, even though additional quantities of divalent metal ions were not added during fermentation or purification steps for the production of Apo-2L. It appears therefore that the presence of zinc or cobalt in a preparation of Apo-2L is inherent to a formulation comprising Apo-2L, and Wiley anticipates the claims.

As for a formulation wherein a divalent ion other than zinc or cobalt is present, it is noted that TRAIL is present in 50mM Na citrate. A review of the composition of Na citrate (Fisher Chemical Catalog, attached) shows that sodium citrate dihydrate (certified) is contaminated with <=0.005% calcium (a divalent metal ion). Therefore there is up to 2.10^{-5} M Ca in a 50mM Na citrate buffer. Wiley is silent as to the amount of protein in the eluate, so the molar ratio of Apo-2L versus

the divalent ion cannot be determined. However, an amount corresponding to 10^{-5} M of Apo-2L would meet the limitations of the claims (this would correspond to a concentration of about 0.28 mg/ml of Apo-2L, assuming that the MW of the 281 amino acid long Apo-2L is 28Kd).

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eliane Lazar-Wesley, PhD, whose telephone number is (703) 305 4059. The examiner can normally be reached on Monday-Friday from 9:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308 4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ELW
May 16, 2002

ELW

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER